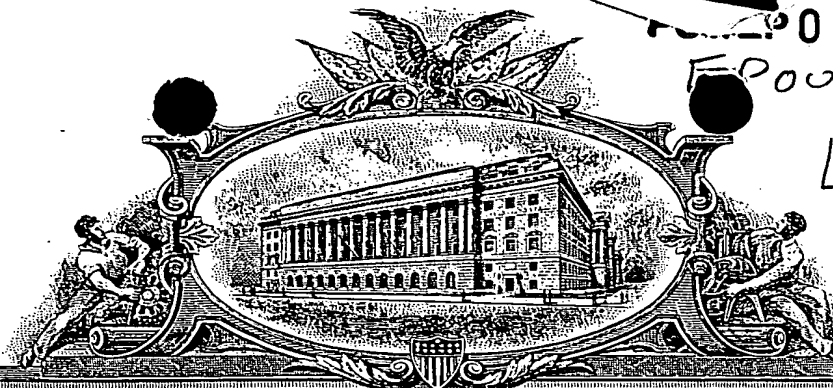


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A0000006L1-01BD

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

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☐ Additional inventors are being named on page 2 attached hereto**TITLE OF THE INVENTION (280 characters max)**

SYNERGISTIC COMBINATIONS OF A NK1-RECEPTOR ANTAGONIST AND A GABA ANALOG

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ENCLOSED APPLICATION PARTS (check all that apply)☒ Specification Number of Pages 21☒ Drawing(s) Number of Sheets 16Other (specify) 18 claims on 3 pages
abstract on 1 page**METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)**☐ A check or money order is enclosed to cover the filing fees☒ The Commissioner is hereby authorized to charge filing fees or
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE Elizabeth M. AndersonDATE October 7, 1999TYPED or PRINTED NAME Elizabeth M. AndersonREGISTRATION NO. 31,585
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SYNERGISTIC COMBINATIONS OF
A NK₁ RECEPTOR ANTAGONIST AND A GABA ANALOG

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SYNERGISTIC COMBINATIONS OF
A NK₁ RECEPTOR ANTAGONIST AND A GABA ANALOG

FIELD OF THE INVENTION

5 This invention relates to a method for preventing and for treating chronic pain through the use of effective amounts of synergistic NK₁ receptor antagonist/GABA analog combinations, and to pharmaceutical compositions useful in said treatment.

BACKGROUND OF THE INVENTION

10 Neurokinin 1 (NK₁) receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinins, and in particular of substance P, an important neurotransmitter in the transmission of pain.

15 A selective NK₁ receptor antagonist, [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester, has been shown in the rat to block the maintenance of streptozocin-induced static allodynia (Field *et al.*, (1998) J. Pharmacol. Exp. Ther. 285: 1226-1232).

20 Gabapentin (1-(aminomethyl)cyclohexane acetic acid) is an antiepileptic drug. This γ -aminobutyric acid (GABA) structural analogue has been shown to possess antihyperalgesic actions in animal models of inflammatory and neuropathic pains, and in particular to block the maintenance of streptozocin-induced static allodynia in the rat (Field *et al.*, (1997) J. Pharmacol. Exp. Ther. 282: 1242-1246).

25 Chronic painful conditions, in various forms, affect a considerable number of people including, according to the World Health Organization, 4 million cancer sufferers who, worldwide, suffer as a result of a lack of suitable care. There are a number of other conditions, such as musculoskeletal or vertebral pain, neurological pain, headaches or vascular pain. Neuropathic pain, a chronic pain condition

occurring in the setting of nervous system injury or tissue injury, is characterized by unusual sensory experiences (allodynia, hyperalgesia) and abnormal pain processing in the central and peripheral nervous systems; treatment of neuropathic pain is difficult. Painful diabetic neuropathy is one of the most frequent complications of diabetes in humans; post-herpetic neuralgia develops in 10-30 % of patients after herpes zoster, phantom limb and stump pain is a common sequela of amputation. Chronic pain may also be caused by a trauma, an entrapment neuropathy (e.g. carpal tunnel syndrome), multiple sclerosis or a polyneuropathy associated with AIDS, alcohol, hypothyroidism, or anticancer chemotherapy.

Conventional treatments of pain fall into two categories: 1) nonsteroidal anti-inflammatory drugs (NSAIDs), used to treat mild pain, but whose therapeutic use is limited by GI adverse effects; 2) morphine and related opioids, used to treat moderate to severe pain but whose therapeutic use is limited by undesirable side effects including respiratory depression, tolerance, and abuse potential. However, conventional analgesics, whether opiates or NSAIDs, have limited therapeutic value in the management of chronic pain syndromes. This has led to the use of adjuvant analgesics for the management of these conditions. For example, tricyclic antidepressants are currently the first choice in the treatment of painful diabetic neuropathy (Galer, 1995; James and Page, 1994). However, no agent is fully effective in all patients and undesirable side effects are common (Galer, 1995; James and Page, 1994).

In view of the multiple organs involved in the presentation of cancer, AIDS, multiple sclerosis, or diabetes, requiring multiple drugs, the treatment of the associated chronic pain warrants careful attention to side effects, contraindications and drug interaction.

To this day, a major problem therefore exists, the resolution of which has been unsatisfactory, for the treatment of chronic pain. In particular, there is a need for drugs that can alleviate chronic pain without undesirable side effects, and for combination therapy with analgesic agents having distinct mechanisms of action, acting in a synergistic manner.

SUMMARY OF THE INVENTION

It has now been discovered that combination therapy with a NK₁ receptor antagonist and a GABA analog results in dramatic improvement in chronic pain control. When administered together, the NK₁ receptor antagonist and the GABA analog can interact in a synergistic manner to control chronic pain. This unexpected synergy allows a reduction in the dose required of each compound, leading to a reduction in the side effects, and enhancement of the clinical utility of the compounds.

Accordingly, this invention provides a method for preventing or treating chronic pain comprising administering to a subject in need of treatment an effective amount of a synergistic combination of a NK₁ receptor antagonist and a GABA analog.

Preferably, the condition treated is selected from causalgia, neuropathic pain, diabetic neuropathy, post-surgery or traumatic neuropathy, postherpetic neuralgia, peripheral neuropathy, entrapment neuropathy, phantom limb and stump pain, neuropathy caused by alcohol abuse, HIV infection, multiple sclerosis, hypothyroidism or anticancer chemotherapy

The invention also concerns a pharmaceutical composition comprising synergistic effective amounts of a NK₁ receptor antagonist and a GABA analog.

The invention also concerns the use of a composition comprising synergistic effective amounts of a NK₁ receptor antagonist and a GABA analog, or pharmaceutically acceptable salts thereof, for the preparation of a medicament useful for preventing or treating chronic pain.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1a. Effect of [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (CI-1021) on the maintenance of diabetes-induced static allodynia.

5 FIGURE 1b. Effect of gabapentin on the maintenance of diabetes-induced static allodynia.

Results are shown as median paw withdrawal thresholds (PWT) measured up to 4 h post *p.o.* drug (vertical bars represent 1st and 3rd quartiles) in 8-10 animals per group.

10 *: $P < 0.05$ **: $P < 0.01$ ***: $P < 0.001$ significantly different from vehicle treated group at each time point.

FIGURE 2a. Dose response 1 h after drug for gabapentin and [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (CI-1021) on the maintenance of diabetes-induced static allodynia.

15 FIGURE 2b. Dose response 1 h after drug for gabapentin and CI-1021 combinations at the fixed dose ratio of 1:1 on the maintenance of diabetes-induced static allodynia.

20 FIGURE 2c. Dose response 1 h after drug for gabapentin and CI-1021 combinations at the fixed dose ratio of 10:1 on the maintenance of diabetes-induced static allodynia.

FIGURE 2d. Dose response 1 h after drug for gabapentin and CI-1021 combinations at the fixed dose ratio of 20:1 on the maintenance of diabetes-induced static allodynia.

25 FIGURE 2e. Dose response 1 h after drug for gabapentin and CI-1021 combinations at the fixed dose ratio of 40:1 on the maintenance of diabetes-induced static allodynia.

FIGURE 2f. Dose response 1 h after drug for gabapentin and CI-1021 combinations at the fixed dose ratio of 60:1 on the maintenance of diabetes-induced static allodynia.

FIGURE 3a. Dose response 1 h after drug for gabapentin and (2-methoxybenzyl)-((2S,3S)-2-phenyl-piperidin-3-yl)-amine on the maintenance of diabetes-induced static allodynia.

FIGURE 3b. Dose response 1 h after drug for gabapentin and (2-methoxybenzyl)-((2S,3S)-2-phenyl-piperidin-3-yl)-amine (CP-99994) combinations at the fixed dose ratio of 20:1 on the maintenance of diabetes-induced static allodynia.

FIGURE 4a. Effect of gabapentin on the maintenance of CCI-induced static allodynia.

FIGURE 4b. Effect of [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethyl carbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (CI-1021) on the maintenance of CCI-induced static allodynia.

FIGURE 5a. Dose response 2 h after drug for gabapentin and for [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (CI-1021) on the maintenance of CCI-induced static allodynia.

FIGURE 5b. Dose response 2 h after drug for gabapentin and CI-1021 combinations at the fixed dose ratio of 5:1.

FIGURE 5c. Dose response 2 h after drug for gabapentin and CI-1021 combinations at the fixed dose ratio of 10:1.

FIGURE 6. Dose response 30 min post drug for [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (CI-1021) in the isolation-induced vocalization model of anxiety in the guinea pig pup. Results are shown as mean % reduction \pm SEM in the number of calls vs. baseline measurements taken before the treatment.

*: $P < 0.05$ vs vehicle group; #: $P < 0.05$ vs their own vehicles (not included in the graph for clarity); Kruskal-Wallis test followed by Mann-Whitney test.

DETAILED DESCRIPTION OF THE INVENTION

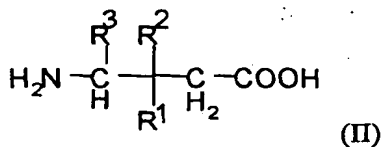
According to this invention, a NK₁ receptor antagonist is used in combination with a GABA analog to treat chronic pain in patients in need of such treatment. The compounds can be employed individually or can be combined in a single formulation, for example as a tablet, capsule, syrup, solution, as well as controlled release formulations. In a preferred embodiment, the NK₁ receptor antagonist and GABA analog are formulated individually and administered in the same manner that each is normally used clinically, but with reduced amounts of each.

The NK₁ receptor antagonists, such as capsaicin, heretofore used to treat pain or a disorder exhibiting a pain component can be used herein. Specific NK₁ receptor antagonists that can be used herein are disclosed in U.S. Patent Nos. 3,862,114, 3,912,711, 4,472,305, 4,481,139, 4,680,283, 4,839,465, 5,102,667, 5,162,339, 5,164,372, 5,166,136, 5,232,929, 5,242,944, 5,300,648, 5,310,743, 5,338,845, 5,340,822, 5,378,803, 5,410,019, 5,411,971, 5,420,297, 5,422,354, 5,446,052, 5,451,586, 5,525,712, 5,527,811, 5,536,737, 5,541,195, 5,594,022, 5,561,113, 5,576,317, 5,604,247, 5,624,950, and 5,635,510; World Patent Application Nos. WO 90/05525, WO 91/09844, WO 91/12266, WO 92/06079, WO 92/12151, WO 92/15585, WO 92/20661, WO 92/20676, WO 92/21677, WO 92/22569, WO 93/00330, WO 93/00331, WO 93/01159, WO 93/01160, WO 93/01165, WO 93/01169, WO 93/01170, WO 93/06099, WO 93/10073, WO 93/14084, WO 93/19064, WO 93/21155, WO 94/04496, WO 94/08997, WO 94/29309, WO 95/11895, WO 95/14017, WO 97/19942, WO 97/24356, WO 97/38692, WO 98/02158, and WO 98/07694; European Patent Application Nos. 284942, 327009, 333174, 336230, 360390, 394989, 428434, 429366, 443132, 446706, 484719, 499313, 512901, 512902, 514273, 514275, 515240, 520555, 522808, 528495, 532456, and 591040. Preferred NK₁ receptor antagonists that can be used herein are disclosed in U.S. Patent No. 5,594,022; among these, a more preferred NK₁ receptor antagonist is [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester.

The GABA analogs heretofore used to treat pain or a disorder exhibiting a pain component can be used herein. Specific GABA analogs that can be used herein are disclosed in U.S. Patent Nos. 4,024,175 and 5,563,175, which are

$$\begin{array}{c}
 \text{H}_2\text{N}-\overset{\text{H}_2}{\underset{|}{\text{C}}}-\overset{\text{H}_2}{\underset{|}{\text{C}}}-\text{CO}_2\text{R}^1 \\
 | \\
 \text{C} \\
 | \\
 (\text{CH}_2)_n
 \end{array}
 \quad (I)$$

In another embodiment, the method for preventing and treating chronic pain of the invention utilizes as a GABA analog a compound of Formula II:



R¹ is straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R³ is hydrogen, methyl, or carboxyl. Diastereoisomers and enantiomers of compounds of Formula II can be utilized in the invention. An especially preferred method of the invention employs as GABA analog a compound of Formula II where R² and R³ are both hydrogen, and R¹ is -(CH₂)₀₋₂-iC₄H₉ as an (R), (S), or (R,S) isomer. A more preferred embodiment of the invention employs, as GABA analog, 3-aminomethyl-5-methyl-hexanoic acid, and especially (S)-3-aminomethyl-

5-methyl-hexanoic acid, known generically as pregabalin. Another preferred compound of Formula II is 3-(1-aminoethyl)-5-methyl-heptanoic acid.

5 The dosage of each agent will vary depending upon the severity of the disease, the frequency of administration, the particular agents, and combinations utilized, and other factors routinely considered by an attending medical practitioner. The NK₁ receptor antagonist is normally administered at a daily dose of from about 0.25 mg to about 500 mg, typically about 3 mg to about 250 mg. The GABA analog is normally administered at doses from about 5 mg to about 2500 mg per day, and more typically from about 50 mg to about 1500 mg per day. 10 A preferred GABA analog is gabapentin, and it is employed at doses from about 100 mg to about 1000 mg per day.

A NK₁ receptor antagonist utilized in the present invention includes solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the NK₁ receptor antagonist.

15 A GABA analog utilized in the present invention includes solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the GABA analog.

20 Where it is appropriate to form a salt of the NK₁ receptor antagonist or of the GABA analog, the pharmaceutically acceptable salts include acetate, benzene-sulfonate, benzoate, bitartrate, calcium acetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycoloylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydrogencarbonate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, 25 malate, maleate, mandelate, mesylate, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate or hemi-succinate, sulfate or hemi-sulfate, tannate, tartrate or hemi-tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, 30 procaine, aluminum, ammonium, tetramethyl ammonium, calcium, lithium, magnesium, potassium, sodium, and zinc. (See also "Pharmaceutical salts" by

Berge S.M. *et al.* (1997) J. Pharm. Sci. 66: 1-19, which is incorporated herein by reference.)

The terms "patient" and "subject" are intended to include a mammal, especially a human.

5 All that is required to practice the method of preventing and treating chronic pain according to the present invention is to administer a synergistic NK₁-GABA analog combination in an amount that is effective to prevent or treat the damaged condition, i.e. to control chronic pain.

10 In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of chronic pain comprising the synergistic NK₁ antagonist - GABA analog combination. Formulating the active components of the combination in dosage unit form with at least one pharmaceutically acceptable carrier or excipient produces pharmaceutical formulations of the composition according to the present invention. For preparing
15 pharmaceutical formulations from the compounds used in this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. They preferably contain 5% to about 70% of the active components of the combination. In such solid dosage forms, the active components
20 are admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for
25 example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i)
30 lubricants, as for example, talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

5 Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose as well as high molecular weight polyethyleneglycols, and the like.

10 Solid dosage forms such as tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They can also be of such composition that they release the active components in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active components of the combination can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

15 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active components of the combination, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, and the like.

20 Suspensions, in addition to the active components, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

25 Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the active components of the combination of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature, and therefore melt in the rectum and release the active components of the combination.

30 Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions of the active components of the combination, and also sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of

suitable liquid carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), and suitable mixtures thereof.

5 These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like can ensure prevention of the action of microorganisms. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like.

10 Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active components of the combination. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it
15 can be the appropriate number of any of these packaged forms. Some examples of dosage unit forms are tablets, capsules, pills, powders, suppositories, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses.

20 The percentage of the active components in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10 % in a solid composition and at least 2 % in a primary liquid composition. The most satisfactory compositions are those in which a much
25 higher proportion of the active components is present, for example, from 10 % to 90 % by weight.

30 Routes of administration of the active components of the combination or their respective salts are parenteral or, preferably, oral. For example, a useful oral dosage is between 20 and 800 mg, expressed as the mass of the GABA analog, and a useful intravenous dose is between 5 and 50 mg. The dosage is within the dosing range used in treatment of pain, or as would be dictated by the needs of the patient as described by the physician.

The invention provides compositions of a NK₁ receptor antagonist and a GABA analog, and a method of treating chronic pain comprising administering to a patient in need of treatment an effective amount of a NK₁ receptor antagonist and an effective amount of a GABA analog. Any NK₁ receptor antagonist can be
5 combined with any GABA analog according to this invention. Preferred GABA analogs to be employed are the compounds of Formula I and II, especially gabapentin and pregabalin. Preferred NK₁ receptor antagonists to be employed in the compositions include (2-methoxy-benzyl)-((2S,3S)-2-phenyl-piperidin-3-yl)-amine, and [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester.
10

When the GABA analog and the NK₁ receptor antagonist are formulated together, the composition contains about 1 to about 1000 parts by weight of GABA analog, and about 1000 to about 1 part by weight NK₁ receptor antagonist. Preferred ranges for the ratio of the two active principles, expressed as parts by
15 weight of the GABA analog relative to parts of the NK₁ receptor antagonist, are 50:1 to 1:1. A most preferred range for the ratio of the two active principles is 20:1. For example, a typical composition of gabapentin and [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester contains about 400 mg of gabapentin and about 20 mg of the NK₁ receptor
20 antagonist. Such combination is administered to an adult patient about twice a day to achieve a synergistic control of chronic pain. The compositions may contain common pharmaceutical excipients such as those described above.

The advantages of using the combination of a NK₁ receptor antagonist and
25 a GABA analog of the instant invention include the selective activity of the combination on chronic pain, the relatively nontoxic nature of the combination, the ease of preparation, the fact that the combination is well tolerated, and the ease of *i.v.* and, in particular, oral administration of the combination.

The ability of synergistic NK₁-receptor antagonist-GABA analog combinations to prevent or treat chronic pain has been established in several animal models.

EXAMPLE 1

Synergistic interaction between a NK₁-receptor antagonist and a GABA analog in animal models of chronic pain

Streptozocin is a selective pancreatic β -cell toxin, which has been used to induce experimental diabetes in laboratory animals (Tomlinson K.C. *et al.*, 1992, Pharmacol Rev 44: 103-150). The resultant loss of endogenous insulin induced by streptozocin mimics the characteristics of type I, or insulin-dependent, diabetes. Streptozocin-induced diabetes has recently been described as a model of chronic pain in rats. It has been reported that streptozocin administration leads to mechanical, thermal, and chemical hyperalgesia as well as mechanical hypersensitivity (Courteix C. *et al.*, 1993, Pain 53: 81-88; Calcutt N.A. *et al.*, 1996, Pain 68: 293-299). The most common symptoms of diabetic neuropathy appear to be spontaneous burning pain and mechanical hypersensitivity in the feet or lower limbs.

The nerve damage induced by chronic constriction injury (CCI) of the sciatic nerve in the rat produces symptoms similar to those displayed in the clinic, mimicking an entrapment neuropathy, such as the carpal tunnel syndrome, with symptoms also evocative of spontaneous pain, like causalgia. An increased sensitivity to a noxious stimulus (hyperalgesia) develops, together with abnormal pain sensations from previously innocuous stimuli (allodynia) (Bennett G.J. and Xie Y.-K., 1988, Pain 33: 87-107; Kim S.H. and Chung J.M., 1992, Pain 50: 355-363).

Methods:

Male Sprague Dawley rats were housed in groups of 6. All animals were kept under a 12-h light/dark cycle (lights on at 07:00 AM) with food and water *ad libitum*. All experiments were carried out by an observer blind to drug treatments.

Development of diabetes in the rat

Diabetes was induced in rats (250–300 g) by a single *i.p.* injection of streptozocin (50 mg/kg) as described previously (Courteix *et al.*, 1993). Control animals received a similar administration of isotonic saline.

5. Induction of chronic constriction injury in the rat

The chronic constriction injury (CCI) was induced as described by Bennett and Xie (1988). Rats were anaesthetized with sodium pentobarbital (60 mg/kg, *i.p.*). The common left sciatic nerve was exposed at the level of the middle of the thigh by blunt dissection through *biceps femoris*, and, proximal to the sciatic's trifurcation, four ligatures (4.0 braided silk) were tied loosely around the nerve with about 1 mm spacing. The muscle was closed in layers, and two wound clips were applied to close the skin incision. The nerve damage due to chronic compression develops within 24 h.

Evaluation of static allodynia

15 Mechanical hypersensitivity was measured using Semmes-Weinstein von Frey hairs. Animals were placed into wire mesh bottom cages allowing access to the underside of their paws. Animals were habituated to this environment prior to the start of the experiment. Mechanical hypersensitivity was tested by touching the plantar surface of the animals' right hind paw with von Frey hairs in ascending order of force (0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1 and 29 g) for up to 6 s. Once a withdrawal response was established, the paw was re-tested, starting with the next descending von Frey hair until no response occurred. The highest force of 29 g lifted the paw as well as eliciting a response, thus represented the cut off point. The paw withdrawal threshold (PWT) was defined as the lowest force (in grams) required to elicit a response.

Drugs used

[2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)], was dissolved in saturated polyglycolysed glycerides (Gelucire™) at a temperature of 65 °C and, once dissolved, maintained at 45 °C. Gabapentin, which is 1-(aminomethyl)cyclohexane acetic acid, and (2-methoxybenzyl)-((2*S*,3*S*)-2-phenylpiperidin-3-yl)-amine, were dissolved in water.

Streptozocin was dissolved in 0.9% w/v NaCl aqueous solution. Drugs were administered under a volume of 1 ml/kg.

Results:

5 Synergistic interaction of gabapentin and [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester on streptozocin-induced static allodynia

Oral administration 1 h before test of either [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (1 - 30 mg/kg) (Figure 1a) or gabapentin (10 - 100 mg/kg) (Figure 1b) dose-dependently
10 blocked the maintenance of static allodynia, with respective minimum effective doses (MED) of 3 and 10 mg/kg.

[2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester and gabapentin were administered at fixed dose ratios of 1:1, 10:1, 20:1, 40:1, and 60:1. The dose response data for both compounds
15 were used to determine theoretical additive lines (Figures 2b to 2f), as described by Berenbaum M.C., 1989, Pharmacol Rev 41: 93-141. Due to the different vehicle used, [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester was administered directly after gabapentin. At a fixed dose ratio of 1:1, combinations of [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester and gabapentin
20 blocked the development of static allodynia, with a complete blockade at the dose of 10:10 mg/kg (Figure 2b). The data was very close to the theoretical additive line indicating an additive interaction (Figure 2b). However, following a fixed dose ratio of 10:1, 20:1 and 40:1, static allodynia was completely blocked by the 10 mg/kg doses. It should be noted that at this dose, neither of the compounds alone showed activity in this model (Figure 2a). The 20:1 ratio was approximately 10 fold more potent than the theoretical additive line (Figure 2d) indicating synergy at this dose ratio.

30 Synergistic interaction of gabapentin and (2-methoxy-benzyl)-((2*S*,3*S*)-2-phenyl-piperidin-3-yl)-amine on streptozocin-induced static allodynia

Oral administration 1 h before test of either (2-methoxy-benzyl)-((2S,3S)-2-phenyl-piperidin-3-yl)-amine (3 - 30 mg/kg) or gabapentin (10 - 100 mg/kg) dose-dependently blocked the maintenance of static allodynia (Figure 3a).

(2-Methoxy-benzyl)-((2S,3S)-2-phenyl-piperidin-3-yl)-amine and gabapentin were administered at the fixed dose ratio of 20:1. The dose response data for both compounds were used to determine the theoretical additive line (Figure 3b). In rats given the combination at the fixed dose ratio of 20:1, static allodynia was completely blocked by the 10-mg/kg dose. Again at this dose, neither of the compounds alone showed such activity in this model. The 20:1 ratio was approximately 3 fold more potent than the theoretical additive line, indicating synergy at this dose ratio.

Synergistic interaction of [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester and gabapentin on CCI-induced static allodynia

Oral administration (10-100 mg/kg) of either gabapentin (Figure 4a) or [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (Figure 4b) also dose-dependently blocked the maintenance of CCI-induced static allodynia with MEDs of 30 mg/kg. The highest dose (100 mg/kg) of gabapentin, but not of [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester, completely blocked static allodynia.

[2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester and gabapentin were administered at fixed dose ratios of 5:1 and 10:1. The dose response data for both compounds were used to determine theoretical additive lines as described by Berenbaum, *Ibidem* (Figure 5b, 5c). Due to the different vehicle used, [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester was administered directly after gabapentin. Two hours after administration as a fixed dose ratio of 5:1, combinations of [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester and gabapentin blocked the development of static allodynia, showing a complete blockade at the

dose of 30:6 mg/kg (Figure 5b). At this dose level, gabapentin alone shows a significant effect but does not produce total blockade, while [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester has no effect (Figure 5a). The 5:1 ratio was approximately 3 fold more potent than the theoretical additive line (Figure 5b) indicating modest synergy at this dose ratio. However, following a fixed dose ratio of 10:1 static allodynia was completely blocked 2 h after administration at the doses 10:1 mg/kg (Figure 5c). It should be noted that at these doses neither of the compounds alone showed activity in this model (Figure 5a). The 10:1 ratio was approximately 10 fold more potent than the theoretical additive line (Figure 5c) indicating synergy at this dose ratio.

Therefore, gabapentin or [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester can block the maintenance of streptozocin- and CCI-induced static allodynia when administered alone. However, when administered together at a combination ratio of 10:1, 20:1 or 40:1, the two compounds can interact in a synergistic manner to block pain, in both neuropathic pain models. The synergy also exists between gabapentin and others NK₁ receptor antagonists such as (2-methoxy-benzyl)-((2*S*,3*S*)-2-phenyl-piperidin-3-yl)-amine. The reduction in dose required of each compound will lead to a reduction in the side effects, and enhance the clinical utility of the compounds.

EXAMPLE 2

Synergistic interaction between a NK₁-receptor antagonist and a GABA analog in isolation-induced vocalizations of guinea-pig pups

Methods:

Distress vocalizations of guinea-pig pups (2-14 days old) are quantified in a 5-min isolation period, after which they are reunited with their mothers and littermates. The test cage consists of a sound-attenuating box with a white interior and white illumination. The vocalizations are recorded by means of a microphone and a digital audio tape (DAT) recorder. Pups are first selected using the criterion of emitting a minimum of 500 vocalizations after three pre-tests on three consecutive days. On the day of the test, pups are submitted to a pre-treatment (baseline)

measurement. Each pup then receives oral administration of test compounds and is returned to the home cage for 30 min before maternal separation.

Different ratios of combinations of doses are administered to groups of animals (n= 9-10 per group). A minimum of 3 total doses for each ratio of combination is examined. The difference in the number of calls emitted before and after treatment is counted using Spike2 software; percentage of reduction in the number of calls is analyzed using a Kruskal-Wallis test followed by Mann-Whitney test between vehicle and different treatments. For example, the oral administration of [2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (0.01-10.0 mg/kg *p.o.*, in Gelucire™ vehicle 30 min before the test) dose-dependently blocked vocalizations with a MED of 1.0 mg/kg (Figure 6). With different ratios of combinations of doses of a NK₁ receptor antagonist and a GABA analog, a synergistic interaction is considered when a significant shift to the left from the additive line is achieved.

The following examples illustrate typical formulations provided by the invention.

EXAMPLE 3

Tablet Formulation

Ingredient	Amount (mg)
[2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)]	5
Gabapentin	100
Lactose	95
Corn starch (for mix)	20
Corn starch (paste)	20
Magnesium stearate (1%)	10
Total	250

5 The benzofuranyl-methyl ester, gabapentin, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 400 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried. The dry granules are lubricated with the 1 % magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of chronic pain.

EXAMPLE 4

Preparation for Oral Solution

Ingredient	Amount
[2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)]	20 mg
Pregabalin	400 mg
Sorbitol solution (70% N.F.)	40 mL
Sodium benzoate	20 mg
Saccharin	5 mg
Red dye	10 mg
Cherry flavor	20 mg
Distilled water q.s.	100 mL

15 The sorbitol solution is added to 40 mL of distilled water, and pregabalin and the benzofuranylmethyl ester are dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water.

EXAMPLE 5

Parenteral Solution

5

1. 1990年	2. 1991年	3. 1992年	4. 1993年	5. 1994年	6. 1995年	7. 1996年	8. 1997年	9. 1998年	10. 1999年	11. 2000年	12. 2001年	13. 2002年	14. 2003年	15. 2004年	16. 2005年	17. 2006年	18. 2007年	19. 2008年	20. 2009年	21. 2010年	22. 2011年	23. 2012年	24. 2013年	25. 2014年	26. 2015年	27. 2016年	28. 2017年	29. 2018年	30. 2019年	31. 2020年	32. 2021年	33. 2022年	34. 2023年	35. 2024年	36. 2025年	37. 2026年	38. 2027年	39. 2028年	40. 2029年	41. 2030年	42. 2031年	43. 2032年	44. 2033年	45. 2034年	46. 2035年	47. 2036年	48. 2037年	49. 2038年	50. 2039年	51. 2040年	52. 2041年	53. 2042年	54. 2043年	55. 2044年	56. 2045年	57. 2046年	58. 2047年	59. 2048年	60. 2049年	61. 2050年	62. 2051年	63. 2052年	64. 2053年	65. 2054年	66. 2055年	67. 2056年	68. 2057年	69. 2058年	70. 2059年	71. 2060年	72. 2061年	73. 2062年	74. 2063年	75. 2064年	76. 2065年	77. 2066年	78. 2067年	79. 2068年	80. 2069年	81. 2070年	82. 2071年	83. 2072年	84. 2073年	85. 2074年	86. 2075年	87. 2076年	88. 2077年	89. 2078年	90. 2079年	91. 2080年	92. 2081年	93. 2082年	94. 2083年	95. 2084年	96. 2085年	97. 2086年	98. 2087年	99. 2088年	100. 2089年	101. 2090年	102. 2091年	103. 2092年	104. 2093年	105. 2094年	106. 2095年	107. 2096年	108. 2097年	109. 2098年	110. 2099年	111. 2100年	112. 2101年	113. 2102年	114. 2103年	115. 2104年	116. 2105年	117. 2106年	118. 2107年	119. 2108年	120. 2109年	121. 2110年	122. 2111年	123. 2112年	124. 2113年	125. 2114年	126. 2115年	127. 2116年	128. 2117年	129. 2118年	130. 2119年	131. 2120年	132. 2121年	133. 2122年	134. 2123年	135. 2124年	136. 2125年	137. 2126年	138. 2127年	139. 2128年	140. 2129年	141. 2130年	142. 2131年	143. 2132年	144. 2133年	145. 2134年	146. 2135年	147. 2136年	148. 2137年	149. 2138年	150. 2139年	151. 2140年	152. 2141年	153. 2142年	154. 2143年	155. 2144年	156. 2145年	157. 2146年	158. 2147年	159. 2148年	160. 2149年	161. 2150年	162. 2151年	163. 2152年	164. 2153年	165. 2154年	166. 2155年	167. 2156年	168. 2157年	169. 2158年	170. 2159年	171. 2160年	172. 2161年	173. 2162年	174. 2163年	175. 2164年	176. 2165年	177. 2166年	178. 2167年	179. 2168年	180. 2169年	181. 2170年	182. 2171年	183. 2172年	184. 2173年	185. 2174年	186. 2175年	187. 2176年	188. 2177年	189. 2178年	190. 2179年	191. 2180年	192. 2181年	193. 2182年	194. 2183年	195. 2184年	196. 2185年	197. 2186年	198. 2187年	199. 2188年	200. 2189年	201. 2190年	202. 2191年	203. 2192年	204. 2193年	205. 2194年	206. 2195年	207. 2196年	208. 2197年	209. 2198年	210. 2199年	211. 2200年	212. 2201年	213. 2202年	214. 2203年	215. 2204年	216. 2205年	217. 2206年	218. 2207年	219. 2208年	220. 2209年	221. 2210年	222. 2211年	223. 2212年	224. 2213年	225. 2214年	226. 2215年	227. 2216年	228. 2217年	229. 2218年	230. 2219年	231. 2220年	232. 2221年	233. 2222年	234. 2223年	235. 2224年	236. 2225年	237. 2226年	238. 2227年	239. 2228年	240. 2229年	241. 2230年	242. 2231年	243. 2232年	244. 2233年	245. 2234年	246. 2235年	247. 2236年	248. 2237年	249. 2238年	250. 2239年	251. 2240年	252. 2241年	253. 2242年	254. 2243年	255. 2244年	256. 2245年	257. 2246年	258. 2247年	259. 2248年	260. 2249年	261. 2250年	262. 2251年	2
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-21-
CLAIMS

What is claimed is:

1. A method for preventing or for treating chronic pain comprising administering to a patient in need of treatment an effective amount of a synergistic combination of a NK₁ receptor antagonist and a GABA analog.
2. A method of Claim 1 wherein the ratio of the GABA analog relative to the NK₁ receptor antagonist is from 50:1 to 1:1 expressed as parts by weight.
3. A method of Claim 1 wherein the ratio of the GABA analog relative to the NK₁ receptor antagonist is 20:1 expressed as parts by weight.
4. A method according to Claim 1 wherein the NK₁ receptor antagonist is [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)].
5. A method according to Claim 1 wherein the GABA analog is gabapentin.
6. A method according to Claim 1 wherein the GABA analog is pregabalin.
7. A method according to Claim 1 employing [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and gabapentin.
8. A method according to Claim 1 employing [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and pregabalin.
9. A method according to Claim 1 wherein the condition treated is selected from causalgia, neuropathic pain, diabetic neuropathy, post-surgery or

traumatic neuropathy, postherpetic neuralgia, peripheral neuropathy, entrapment neuropathy, phantom limb and stump pain, neuropathy caused by alcohol abuse, HIV infection, multiple sclerosis, hypothyroidism or anticancer chemotherapy.

- 5 10. A pharmaceutical composition comprising synergistic effective amounts of a NK_1 receptor antagonist and a GABA analog.
11. A composition of Claim 10 wherein the ratio of the GABA analog relative to the NK_1 receptor antagonist is from 50:1 to 1:1 expressed as parts by weight.
- 10 12. A composition of Claim 10 wherein the ratio of the GABA analog relative to the NK_1 receptor antagonist is 20:1 expressed as parts by weight.
13. A composition of Claim 10 wherein the NK_1 receptor antagonist is [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester, [R-(R*,S*)].
- 15 14. A composition of Claim 10 wherein the GABA analog is gabapentin.
15. A composition of Claim 10 wherein the GABA analog is pregabalin.
16. A composition of Claim 10 employing [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and gabapentin.
- 20 17. A composition of Claim 1 employing [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and pregabalin.

18. The use of a composition comprising synergistic effective amounts of a NK_1 receptor antagonist and a GABA analog, or pharmaceutically acceptable salts thereof, for the preparation of a medicament useful for preventing or treating chronic pain.

SYNERGISTIC COMBINATIONS OF
A NK₁ RECEPTOR ANTAGONIST AND A GABA ANALOG

ABSTRACT

5 The present invention provides methods of treatment using synergistic combinations of a NK₁ receptor antagonist and a GABA analog, and pharmaceutical compositions and products containing the NK₁ receptor antagonist and GABA analog.

10 The present invention also provides the use of a NK₁ receptor antagonist and a GABA analog for the manufacture of a medicament for the treatment or prevention of chronic pain,

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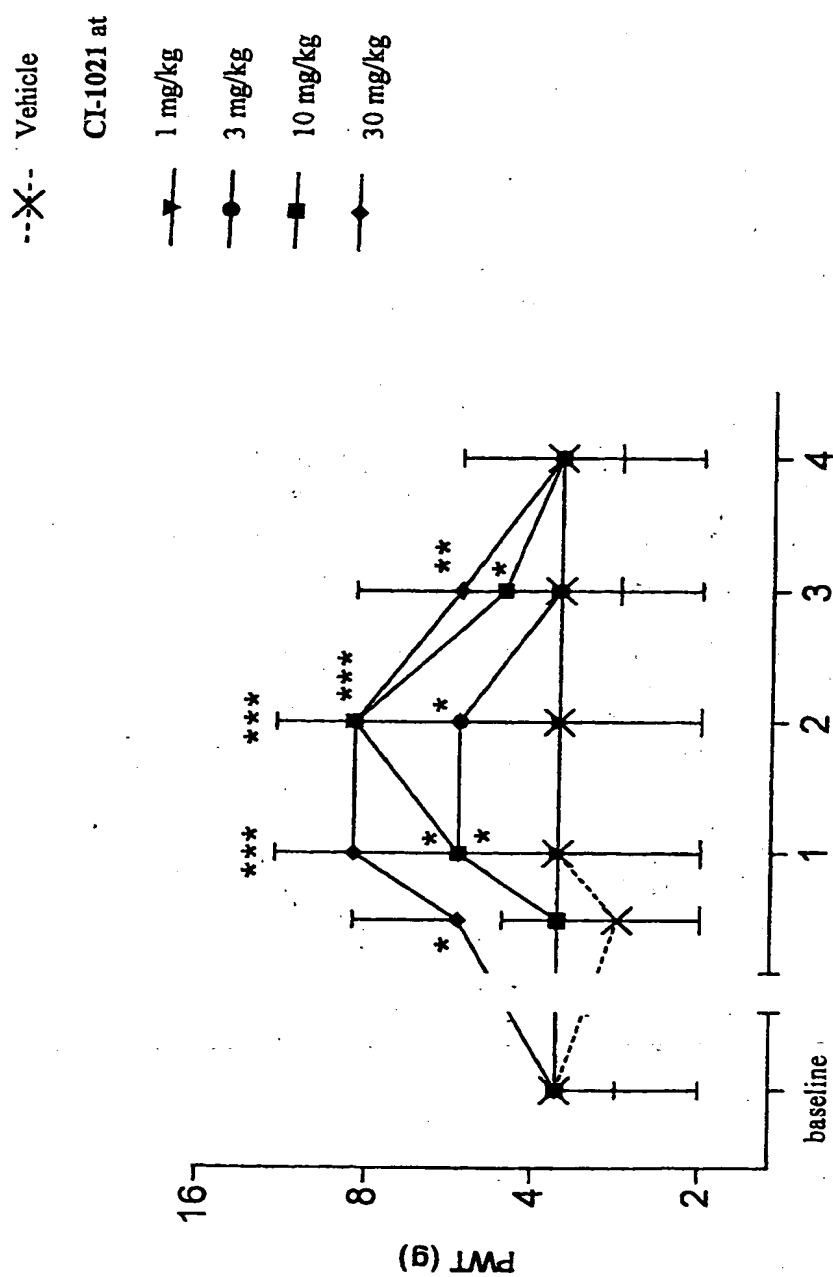


Fig. 1b: Time after gabapentin (h)

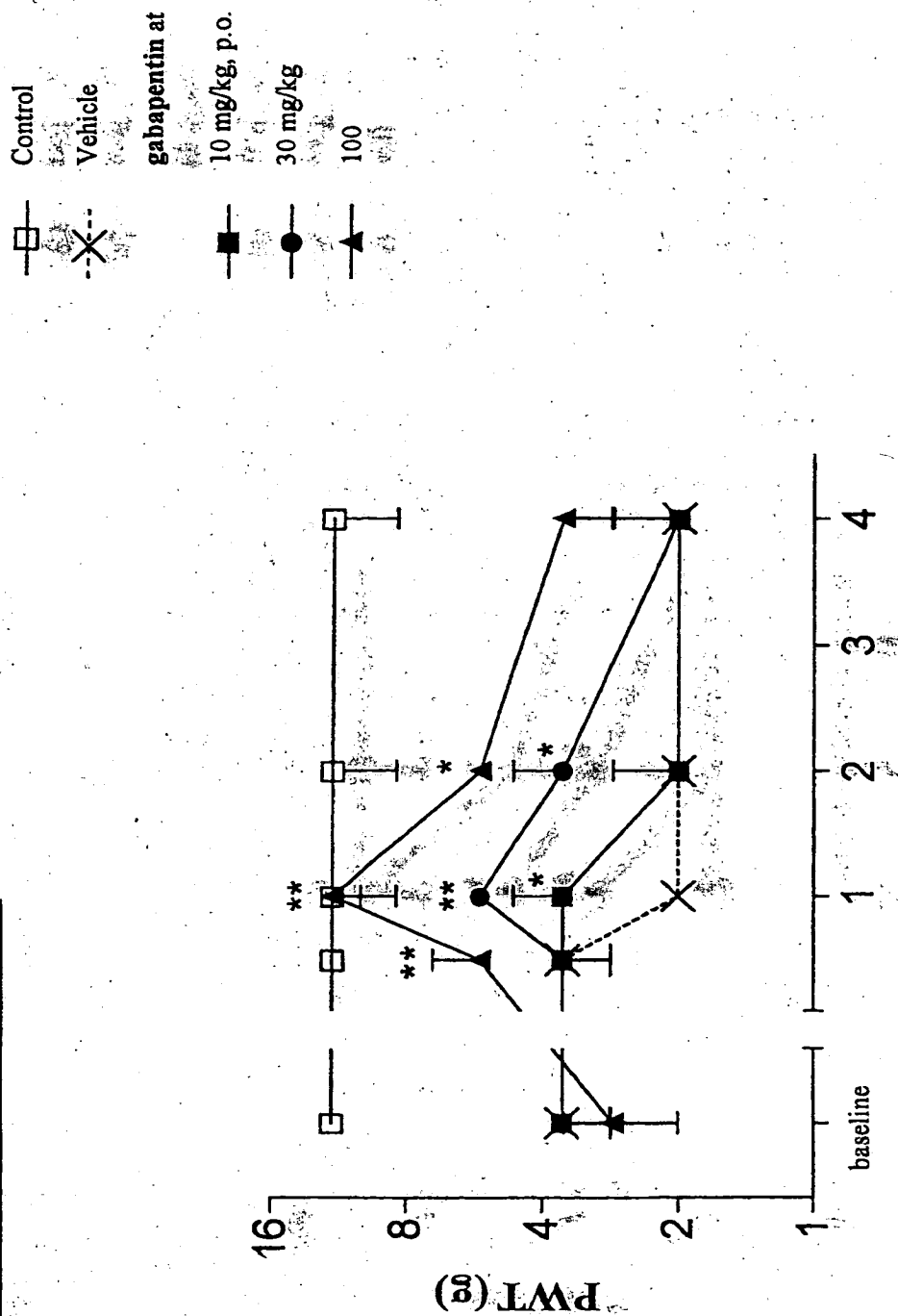


Fig. 2a : Dose responses for gabapentin/CI-1021 (1 h)

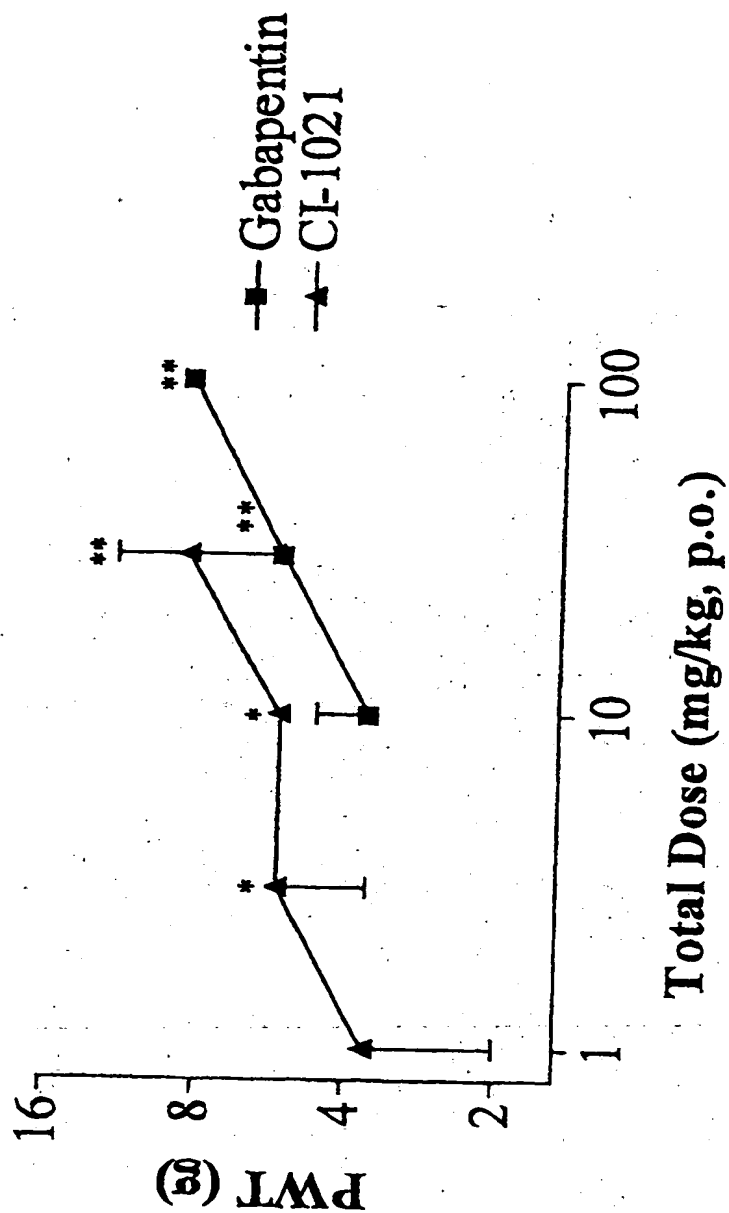


Fig. 2b : 1:1 gabapentin/CI-1021 (1 h)

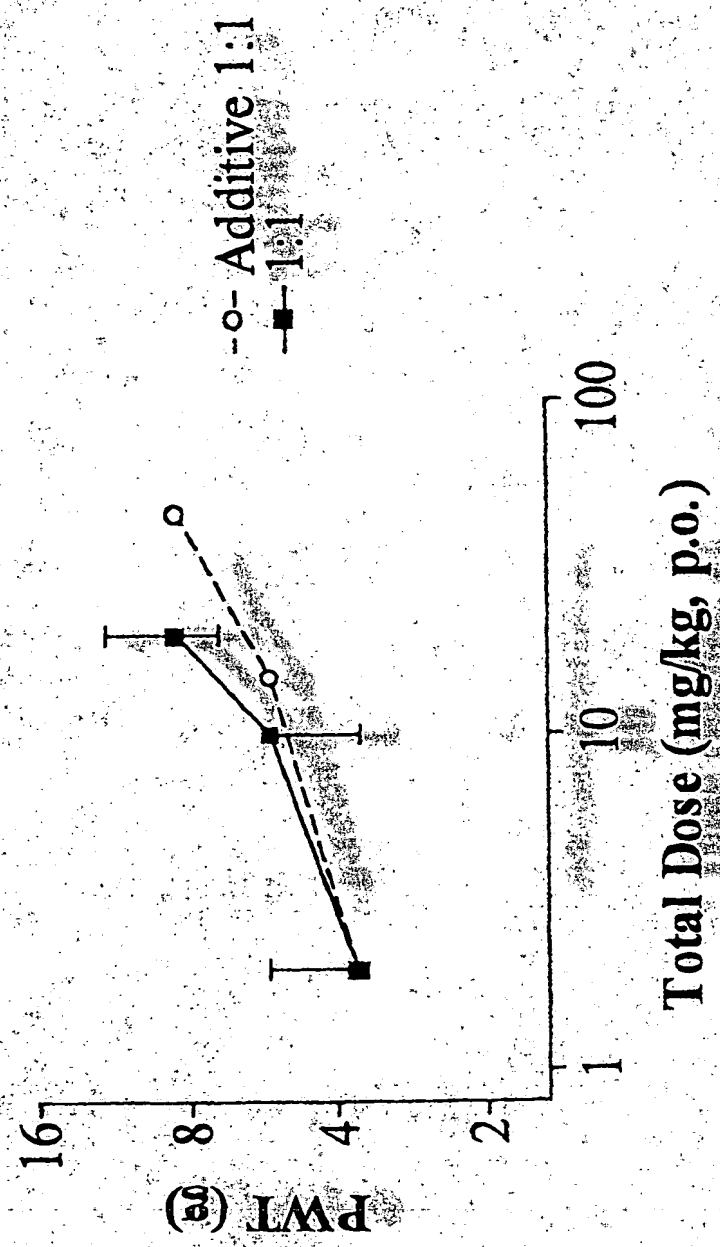


Fig. 2c: 10:1 gabapentin/CI-1021 (1 h)

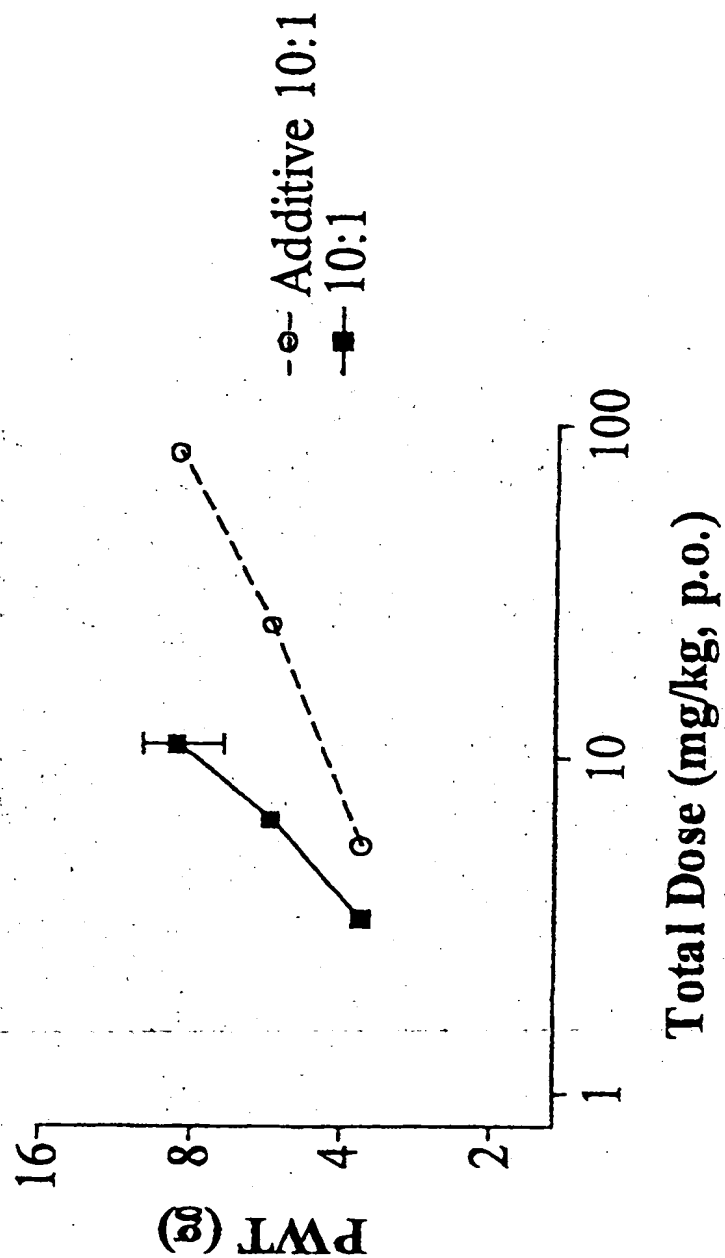


Fig. 2d : 20:1 gabapentin/CI-1021 (1.h)

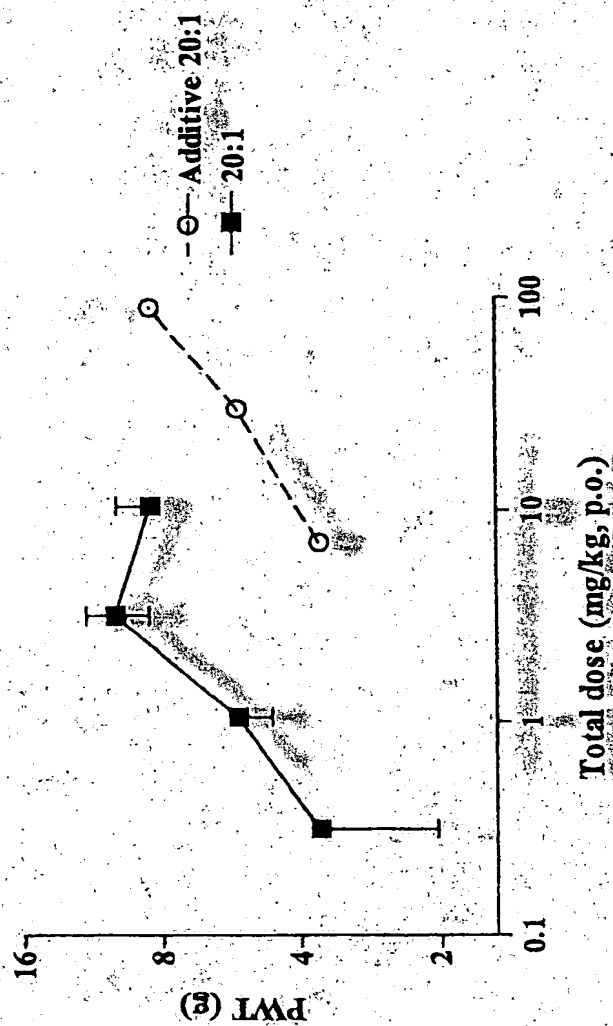


Fig. 2e: 40:1 gabapentin/CI-1021 (1 h)

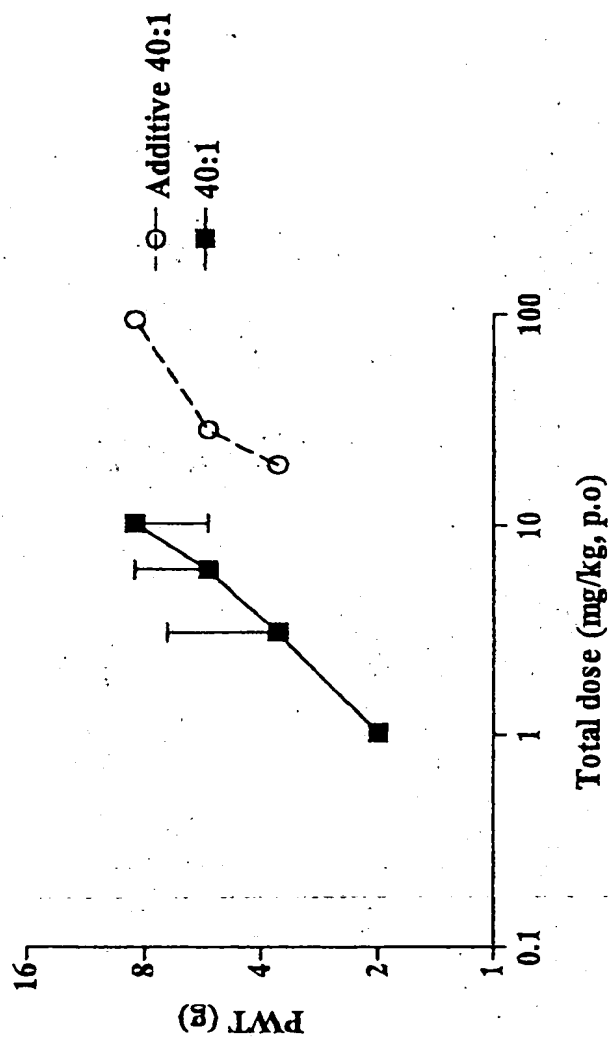


Fig. 2f: 60:1 gabapentin/CI-1021 (1 h)

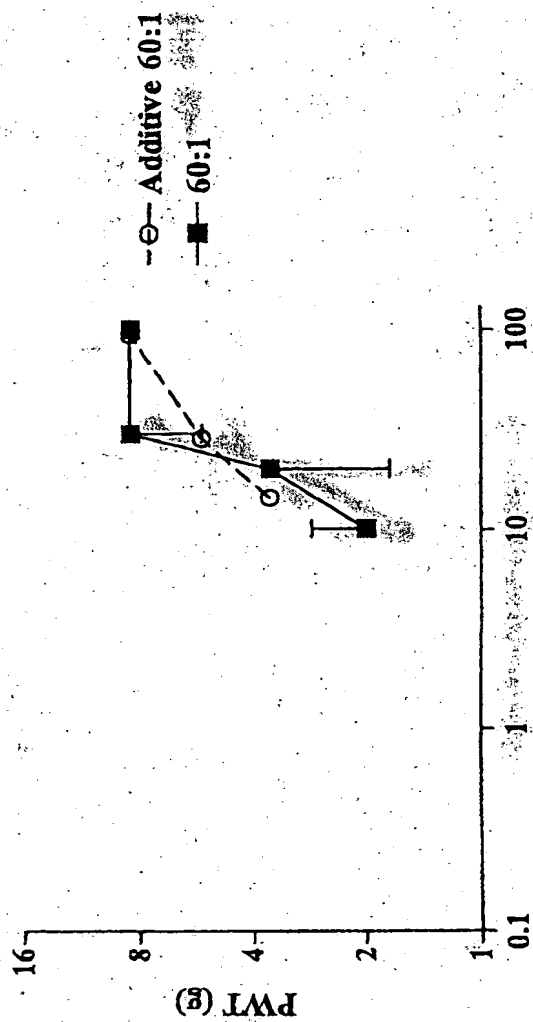
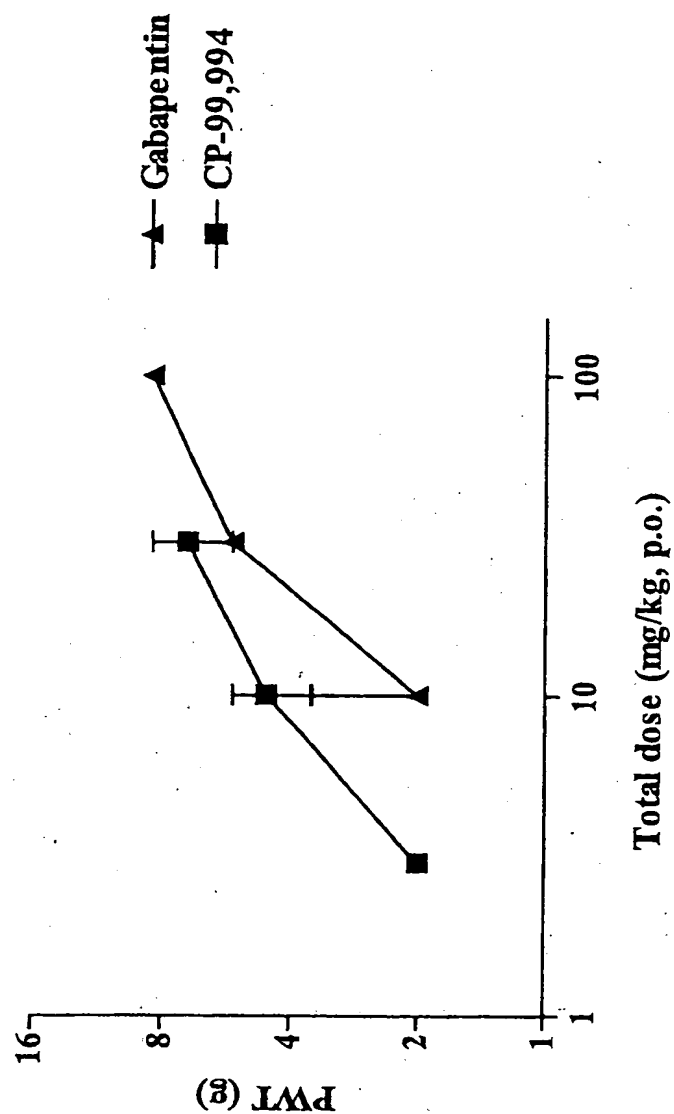


Fig. 3a : Dose responses for gabapentin and CP-99,994



002001 12285409

Fig. 3b: 20:1 gabapentin/CP-99,994 (1 h)

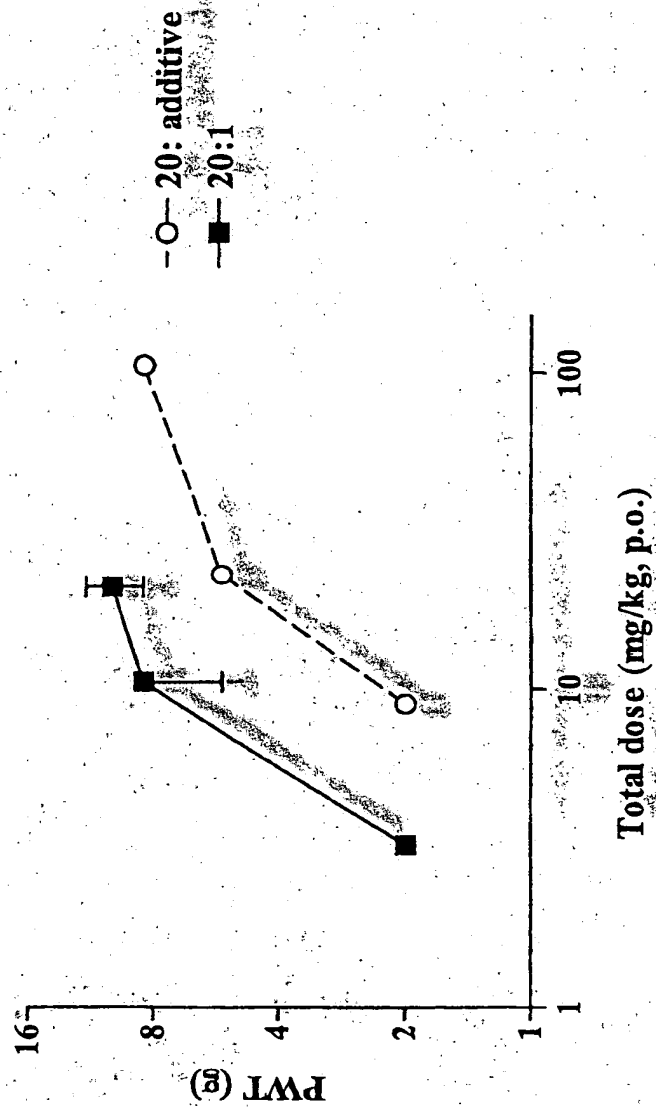


Fig. 4a :

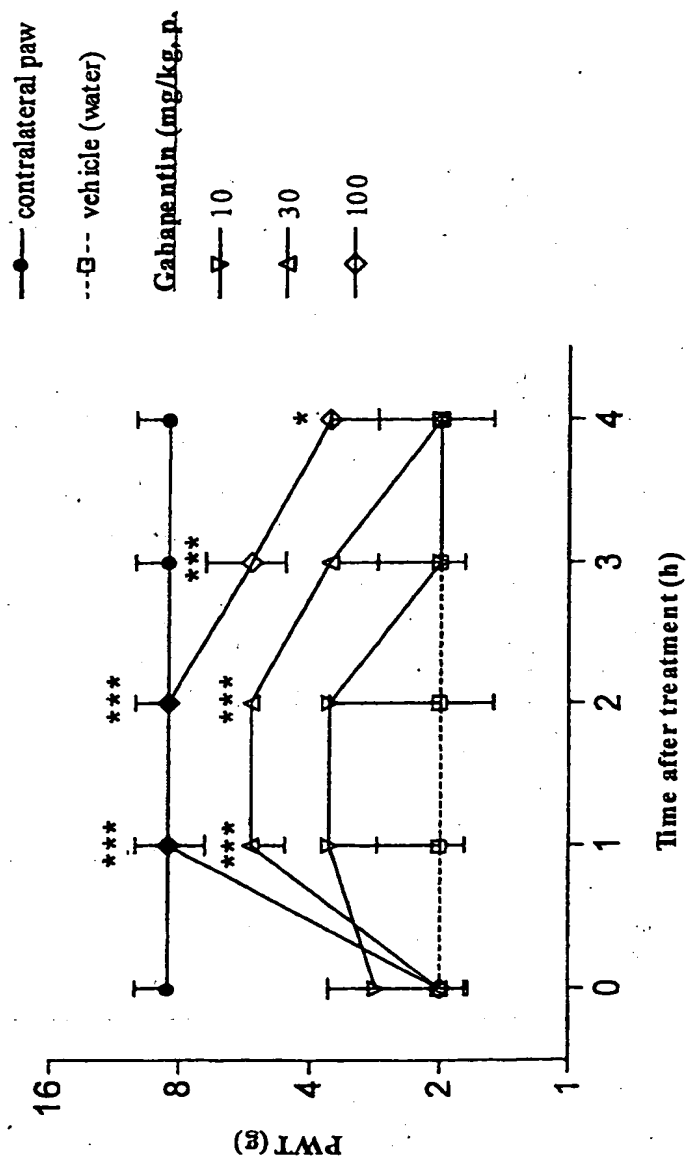


Fig. 4b :

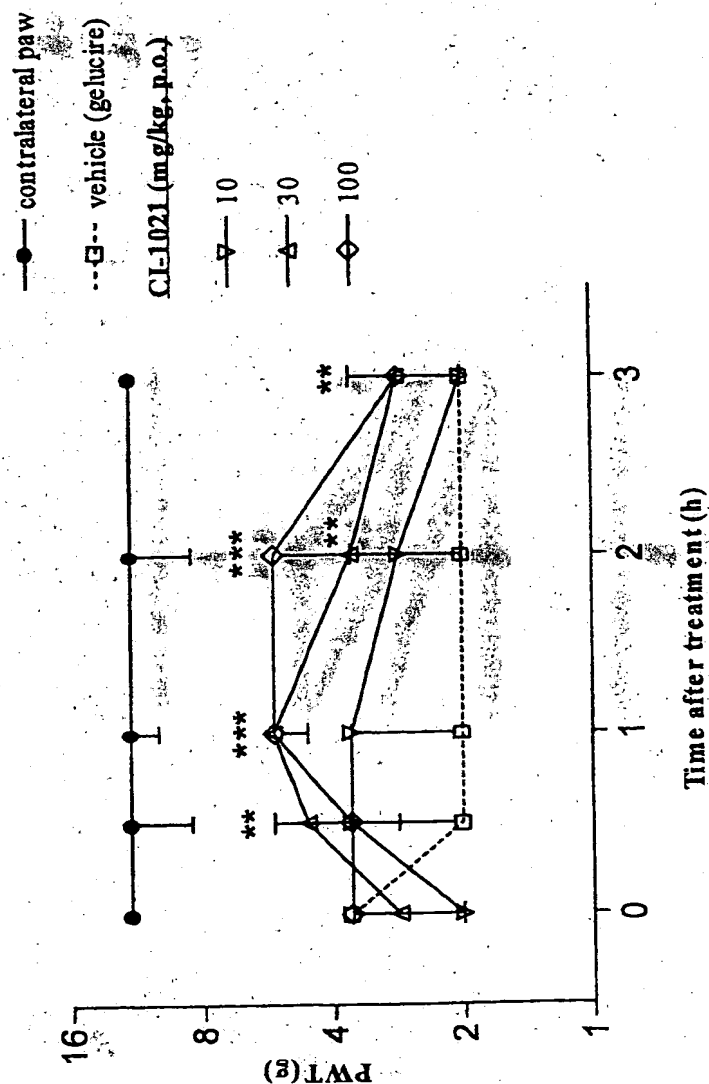


Fig. 5a : Dose responses for gabapentin and CI-1021 (2 h)

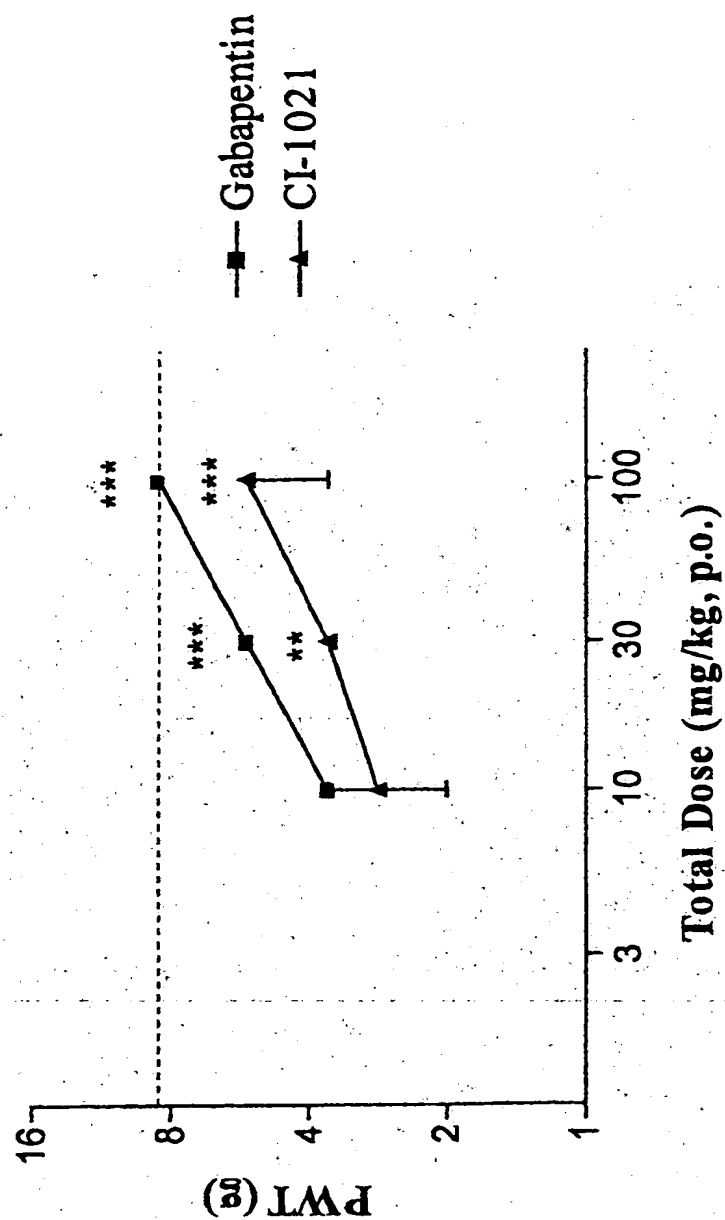


Fig. 5b: 5:1 gabapentin/CI-1021 (2 h)

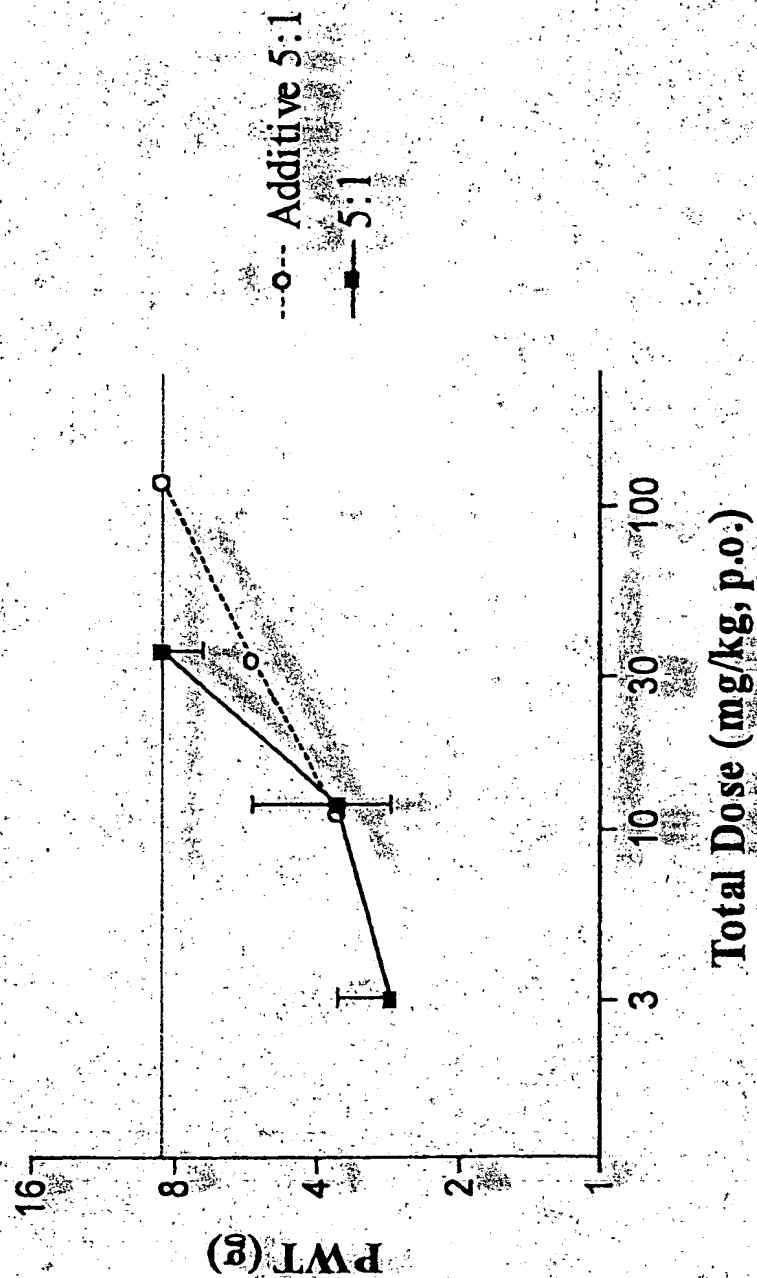


Fig. 5c: 10:1 gabapentin/CI-1021 (2 h)

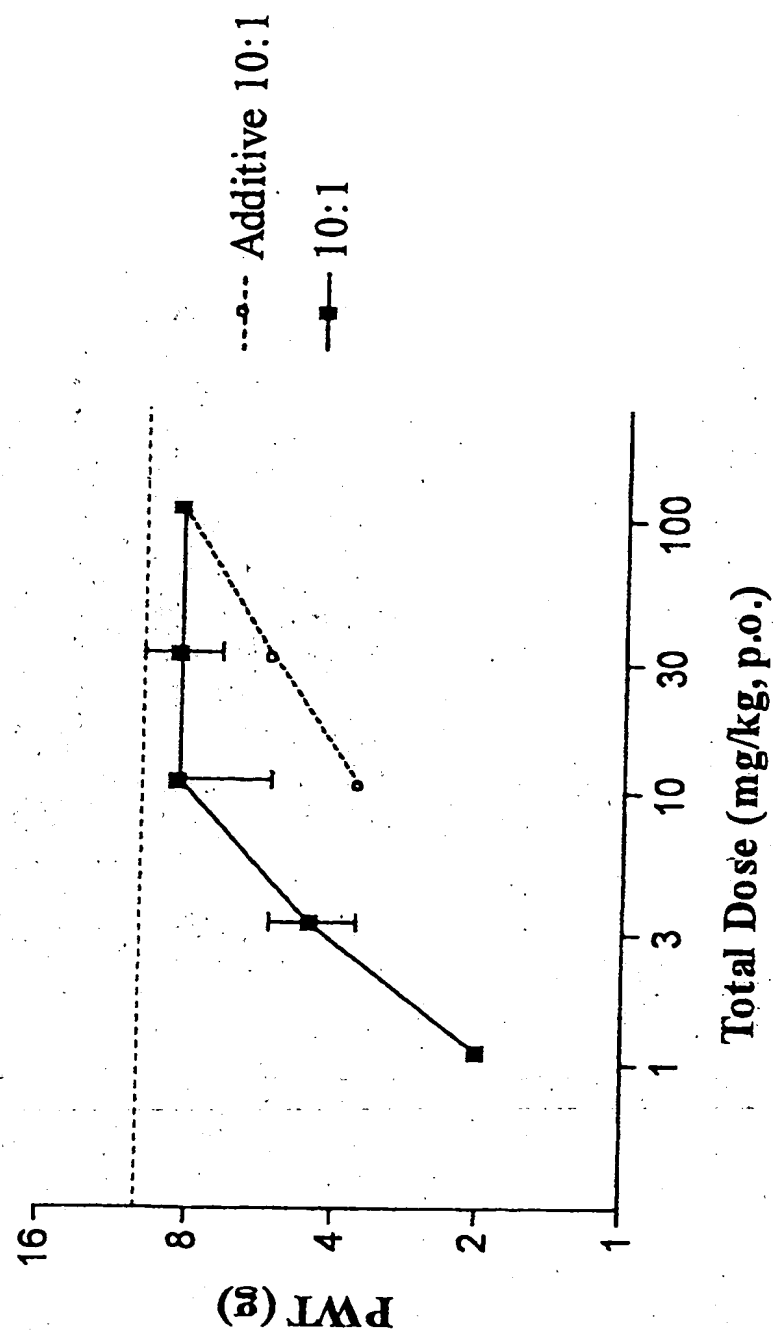


Fig.6 :

